Predictive Value of Blood Pressure Variability Combined with Coagulation Function for Germinal Matrix-Intraventricular Hemorrhage and Its Prognosis in Preterm Infants with Gestational Age $\leq$ 32 Weeks: A Postprint Study

Authors: Jiang Lijun, Yu Qian, Wang Fudong, Guo Wei, Guo Wei

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Abstract

Background: Germinal matrix-intraventricular hemorrhage (GMH-IVH) is a major cause of neurological sequelae in preterm infants. Early prediction of GMH-IVH and comprehensive management are particularly important for improving the prognosis of preterm infants. Disturbances in cerebral blood flow (CBF) caused by blood pressure fluctuations and increased hemorrhage risk due to immature coagulation function are important pathogenic factors for GMH-IVH.

Objective: To analyze whether combined detection of blood pressure variability (BPV) and coagulation function can early predict the occurrence of GMH-IVH in preterm infants with gestational age $ $32 weeks, and to evaluate their short-term prognosis.

Methods: A total of 106 preterm infants with gestational age $ $32 weeks who were hospitalized in the Neonatal Intensive Care Unit of the Affiliated Hospital of Yangzhou University between June 2022 and June 2024 and met the criteria were selected as study subjects. According to the presence or absence of GMH-IVH, preterm infants were divided into: GMH-IVH group (51 cases) and non-GMH-IVH group (55 cases); according to short-term outcomes, preterm infants were divided into: favorable outcome group (30 cases) and unfavorable outcome group (21 cases). General information and perinatal clinical data of the enrolled preterm infants were collected, coagulation function and BPV parameters of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were monitored in each group, and the relationship between each parameter and GMH-IVH was analyzed. Binary logistic regression analysis was used to explore

risk factors for GMH-IVH and poor outcomes in preterm infants, receiver operating characteristic (ROC) curves were plotted to predict GMH-IVH and poor outcomes in preterm infants, and the area under the ROC curve (AUC) was calculated.

Results: A total of 106 preterm infants were included, including 43 males (40.6%) and 63 females (59.4%). Binary logistic regression analysis showed that increased international normalized ratio (INR) (OR=5.608, 95%CI=2.858~8.587, P=0.003) and increased standard deviation (SD) of DBP (OR=1.455, 95%CI=1.003~2.111, P=0.038) were independent risk factors for GMH-IVH in preterm infants; the AUC for combined prediction of GMH-IVH in preterm infants by INR and SD of DBP was 0.803, with sensitivity of 82.4% and specificity of 79.7%. Binary logistic regression analysis showed that increased INR (OR=3.942, 95%CI=1.509~6.680, P=0.025) and increased SD of DBP (OR=2.334, 95%CI=1.013~5.378, P=0.047) were risk factors for poor outcomes in preterm infants with GMH-IVH; the AUC for combined prediction of poor outcomes in preterm infants with GMH-IVH by INR and SD of DBP was 0.864, with sensitivity of 76.2% and specificity of 90.0%.

Conclusion: Increased INR and SD of DBP are risk factors for GMH-IVH and poor short-term prognosis in preterm infants, and combined monitoring of INR and SD of DBP has certain clinical value for early identification and prognosis prediction of GMH-IVH in preterm infants.

Full Text

Predictive Value of Blood Pressure Variability Combined with Coagulation Function for Germinal Matrix-Intraventricular Hemorrhage and Its Prognosis in Preterm Infants with Gestational Age $\leq$ 32 Weeks

JIANG Lijun[1], YU Qian[2], WANG Fudong[1], GUO Wei[1]*

[1]Affiliated Hospital of Yangzhou University, Yangzhou 225001, China
[2]Dalian Medical University, Dalian 116000, Liaoning Province, China

Corresponding author: GUO Wei, Chief physician; E-mail: klose1981@126.com

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Abstract

Background: Germinal matrix-intraventricular hemorrhage (GMH-IVH) is a leading cause of neurological sequelae in preterm infants. Early prediction and comprehensive management of GMH-IVH are crucial for improving prognosis. Cerebral blood flow (CBF) disturbances caused by blood pressure fluctuations and increased bleeding risk due to immature coagulation function are important pathogenic factors for GMH-IVH.

Objective: To analyze whether combined monitoring of blood pressure variability (BPV) and coagulation function can early predict GMH-IVH occurrence in preterm infants with gestational age ≤ 32 weeks and evaluate its short-term prognosis.

Methods: A total of 106 preterm infants with gestational age ≤ 32 weeks who were admitted to the Neonatal Intensive Care Unit (NICU) of Affiliated Hospital of Yangzhou University between June 2022 and June 2024 and met the inclusion criteria were enrolled. According to the presence or absence of GMH-IVH, preterm infants were divided into the GMH-IVH group (51 cases) and non-GMH-IVH group (55 cases); according to short-term outcomes, they were divided into the good outcome group (30 cases) and poor outcome group (21 cases). General data and perinatal case data of enrolled preterm infants were collected, coagulation function and BPV indices of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were monitored in each group, and the relationship between each index and GMH-IVH was analyzed. Binary Logistic regression analysis was used to explore risk factors for GMH-IVH and poor outcomes in preterm infants, receiver operating characteristic (ROC) curves for risk factors predicting GMH-IVH and poor outcomes were plotted, and the area under the ROC curve (AUC) was calculated.

Results: A total of 106 preterm infants were enrolled, including 43 males (40.6%) and 63 females (59.4%). Binary Logistic regression analysis showed that elevated international normalized ratio (INR) (OR=5.608, 95%CI=2.858-8.587, P=0.003) and standard deviation (SD) of DBP (OR=1.455, 95%CI=1.003-2.111, P=0.038) were independent risk factors for GMH-IVH in preterm infants; the AUC for combined prediction of GMH-IVH using INR and DBP SD was 0.803, with sensitivity of 82.4% and specificity of 79.7%. Binary Logistic regression analysis showed that elevated INR (OR=3.942, 95%CI=1.509-6.680, P=0.025) and DBP SD (OR=2.334, 95%CI=1.013-5.378, P=0.047) were risk factors for poor outcomes of GMH-IVH; the AUC for combined prediction of poor outcomes using INR and DBP SD was 0.864, with sensitivity of 76.2% and specificity of 90.0%.

Conclusion: Elevated INR and DBP SD are risk factors for the occurrence of GMH-IVH and its poor short-term prognosis in preterm infants. Combined monitoring of INR and DBP SD has certain clinical value for early identification and prognosis prediction of GMH-IVH in preterm infants.

Keywords: Cerebral intraventricular hemorrhage; Germinal matrix-intraventricular hemorrhage; Preterm infant; Blood coagulation; Blood pressure; Blood pressure variability

1 Materials and Methods

In recent years, with advances in neonatal intensive care unit (NICU) technology, the survival rate of preterm infants has continuously improved. However, the incidence of germinal matrix-intraventricular hemorrhage (GMH-IVH) in very low birth weight infants has not decreased, which can lead to poor neurodevelopmental outcomes and even death in preterm infants [1]. GMH-IVH in preterm infants has insidious manifestations that can easily lead to missed clinical diagnosis. Therefore, early assessment and comprehensive measures to prevent GMH-IVH are extremely important for improving patient outcomes.

In the pathogenesis of GMH-IVH in preterm infants, cerebral blood flow (CBF) disturbances and increased bleeding risk due to immature coagulation function are important factors [2-3]. Currently, accurate clinical assessment of CBF is difficult. Continuous blood pressure monitoring can indirectly reflect CBF status, but blood pressure is regulated and influenced by numerous factors, making it impossible to evaluate precise changes in CBF. Blood pressure variability (BPV) refers to the degree of continuous blood pressure changes under the influence of external factors. Compared with simple blood pressure monitoring, BPV can more accurately reflect the hemodynamic status of tissues and organs [4]. Clinical studies have found that BPV is an important risk factor for cardiovascular and cerebrovascular events, target organ damage, and poor prognosis in adults [5], but its relationship with the occurrence and outcome of GMH-IVH in preterm infants remains unclear.

It is hypothesized that BPV can evaluate CBF dynamic status to a certain extent, while coagulation index analysis can reflect the potential bleeding risk in preterm infants. The combination of both may facilitate prediction and prognosis evaluation of GMH-IVH, in order to provide guidance for the prevention and management of GMH-IVH in preterm infants.

1.1 Study Subjects

A total of 106 preterm infants who were hospitalized in the NICU of Affiliated Hospital of Yangzhou University between June 2022 and June 2024 and met the criteria were selected as study subjects. Inclusion criteria: (1) admission within 0.5 hours after birth; (2) gestational age $\leq$ 32 weeks; (3) normal platelet count, no treatment with anticoagulant drugs or vasoactive agents. Exclusion criteria: (1) congenital abnormal brain structure development; (2) congenital coagulation factor abnormalities; (3) central nervous system infection; (4) genetic metabolic diseases. This study was approved by the Ethics Committee of Affiliated Hospital of Yangzhou University (2022-YKL3-06-005) and followed medical ethical requirements. As this was a retrospective study, the requirement for informed consent was waived.

1.2 Study Grouping

According to the presence or absence of GMH-IVH, preterm infants were divided into the GMH-IVH group (51 cases) and non-GMH-IVH group (55 cases). According to short-term outcomes, they were divided into the good outcome group (30 cases) and poor outcome group (21 cases).

1.3 Data Collection and Monitoring

General data and perinatal case data of enrolled preterm infants were collected. Cranial ultrasound screening for GMH-IVH was performed using a bedside color Doppler ultrasound diagnostic instrument on days 1, 3, and 7 after birth, and diagnosis and grading were conducted according to the Papile criteria [6].

Coagulation function and BPV monitoring: Within 24 hours after birth, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen (FIB), and D-dimer (DD) were measured. BPV indices: Within 3 days after admission, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured every 3 hours in a quiet state, with monitoring frequency increased to 1 hour when blood pressure was abnormal. The difference between maximum and minimum (Max-min), coefficient of variation (CV), standard deviation (SD), and successive variation (SV) of BPV were used as BPV indices [7-8].

Neurodevelopmental assessment: At a corrected gestational age of 40-42 weeks, cranial magnetic resonance imaging (MRI) and neonatal behavioral neurological assessment (NBNA) were performed. Indicators of poor short-term outcome included brain damage such as reduced periventricular white matter volume, cystic changes, ventricular dilation and hydrocephalus, thinning of the corpus callosum on MRI, and NBNA score <37 [9-10].

1.4 Statistical Methods

SPSS 26.0 software was used for data analysis. Normally distributed measurement data were expressed as ($\bar{x}\pm s$), and independent samples t-test was used for inter-group comparison; non-normally distributed data were expressed as M(Q1, Q3), and Mann-Whitney U test was used for inter-group comparison; count data were expressed as cases (%), and 2 test was used for data comparison. Binary Logistic regression analysis was performed for risk factors of GMH-IVH and poor outcomes in preterm infants, receiver operating characteristic (ROC) curves for risk factors predicting GMH-IVH and poor outcomes were plotted, and the area under the curve (AUC) was calculated. $P<0.05$ was considered statistically significant.

2 Results

2.1 Comparison of General Data

A total of 106 preterm infants with gestational age ≤ 32 weeks who met the criteria were enrolled, including 43 males (40.6%) and 63 females (59.4%), with a mean gestational age of (29.0$±2.3)*weeksandameanbirthweightof*(1234.4±$285.6) g. The proportion of premature rupture of membranes (PROM) in the GMH-IVH group was higher than that in the non-GMH-IVH group, with a statistically significant difference (P<0.05). There were no statistically significant differences between the two groups in gestational age, birth weight, gender, vaginal delivery, multiple births, small for gestational age, 5-minute Apgar score $ $7, maternal hypertension, maternal diabetes, invasive ventilation, prenatal dexamethasone use, or patent ductus arteriosus (PDA) (P>0.05), see Table 1 .

2.2 Analysis of GMH-IVH Risk Factors

2.2.1 Univariate Analysis of Coagulation Function and GMH-IVH PT, INR, and APTT in the GMH-IVH group were all higher than those in the non-GMH-IVH group, with statistically significant differences (P<0.05). There were no statistically significant differences in FIB and DD between the two groups (P>0.05), see Table 2 .

2.2.2 Univariate Analysis of BPV and GMH-IVH The Max-min, SD, and CV of both SBP and DBP in the GMH-IVH group were higher than those in the non-GMH-IVH group, while the mean DBP in the GMH-IVH group was lower than that in the non-GMH-IVH group, with statistically significant differences (P<0.05). There were no statistically significant differences in mean SBP, SV of SBP, or SV of DBP between the two groups (P>0.05), see Table 3 .

2.2.3 Binary Logistic Regression Analysis of GMH-IVH Risk Factors With the occurrence of GMH-IVH in preterm infants as the dependent variable (assignment: yes=1, no=0), and the above statistically significant indicators including PROM (assignment: yes=1, no=0), PT, INR, APTT, SBP (Max-min, SD, CV), and DBP (mean, Max-min, SD, CV) as independent variables (all assigned as measured values), binary Logistic regression analysis was performed. The results showed that elevated INR (OR=5.608, 95%CI=2.858-8.587, P=0.003) and DBP SD (OR=1.455, 95%CI=1.003-2.111, P=0.038) were independent risk factors for GMH-IVH in preterm infants, see Table 4 .

2.2.4 Predictive Value Analysis of INR, DBP SD, and Their Combination for GMH-IVH ROC curve analysis showed that the AUCs for INR, DBP SD, and their combination in predicting GMH-IVH in preterm infants were 0.764, 0.727, and 0.803, respectively, with sensitivities of 72.5%, 78.4%, and 82.4%, and specificities of 70.9%, 68.5%, and 79.7%, respectively, see Table 5 and Figure 1 [Figure 1: see original paper].

2.3 Analysis of GMH-IVH Outcome Risk Factors

2.3.1 Univariate Analysis of Coagulation Function and GMH-IVH Outcomes INR and APTT in the poor outcome group of GMH-IVH were higher than those in the good outcome group, with statistically significant differences (P<0.05). There were no statistically significant differences in PT, FIB, and DD between the two groups (P>0.05), see Table 6 .

2.3.2 Univariate Analysis of BPV and GMH-IVH Outcomes The SD and CV of both SBP and DBP in the poor outcome group of GMH-IVH were higher than those in the good outcome group, while the mean DBP in the poor outcome group was lower than that in the good outcome group, with statistically significant differences (P<0.05). There were no statistically significant differences in mean SBP, Max-min of SBP, SV of SBP, or Max-min and SV of DBP between the two groups (P>0.05), see Table 7 .

2.3.3 Binary Logistic Regression Analysis of Risk Factors for Poor GMH-IVH Outcomes With the outcome of GMH-IVH in preterm infants as the dependent variable (assignment: poor outcome=1, good outcome=0), and the above statistically significant indicators including INR, APTT, SBP (SD, CV), and DBP (mean, SD, CV) as independent variables (all assigned as measured values), binary Logistic regression analysis was performed. The results showed that elevated INR (OR=3.942, 95%CI=1.509-6.680, P=0.025) and DBP SD (OR=2.334, 95%CI=1.013-5.378, P=0.047) were risk factors for poor outcomes of GMH-IVH in preterm infants, see Table 8 .

2.3.4 Predictive Value Analysis of INR, DBP SD, and Their Combination for Poor GMH-IVH Outcomes ROC curve analysis showed that the AUCs for INR, DBP SD, and their combination in predicting poor outcomes of GMH-IVH in preterm infants were 0.808, 0.773, and 0.864, respectively, with sensitivities of 61.9%, 81.0%, and 76.2%, and specificities of 96.7%, 66.7%, and 90.0%, respectively, see Table 9 and Figure 2 [Figure 2: see original paper].

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3 Discussion

The occurrence of GMH-IVH involves multiple harmful factors: (1) fragile vascular structure of the germinal matrix; (2) CBF disturbances caused by abnormal cerebrovascular autoregulation (CAR); and (3) increased bleeding risk due to coagulation dysfunction [11-13]. Previous studies have found that the smaller the gestational age and the lower the birth weight, the higher the risk of GMH-IVH, and perinatal factors before, during, and after delivery may all affect the occurrence of GMH-IVH in preterm infants [14-17]. This study analyzed the influence of perinatal factors on GMH-IVH in preterm infants. Due to the relatively small number of included preterm infants with small gestational ages, gestational age

and birth weight were not significant influencing factors, but PROM was an important factor. PROM is closely related to congenital infection. After membrane rupture, the fetus loses its natural protective barrier, increasing the risk of pathogen invasion [18]. Therefore, the risk of perinatal infection in newborns is significantly increased when PROM occurs [19]. Studies have shown that systemic pro-inflammatory factor activation during perinatal infection affects the coagulation balance mechanism. For example, increased pro-inflammatory factors such as interleukin-6 (IL-6) are closely related to coagulation dysfunction and GMH-IVH occurrence [18].

In previous studies, abnormal APTT and DD were associated with hemorrhagic disease in preterm infants [20], and elevated INR within 48 hours after birth may help identify preterm infants at risk for intracranial hemorrhage [21]. The study by SIDDAPPA et al. [22] also confirmed that infants with severe intraventricular hemorrhage had longer PT and higher INR. This study similarly found that PT, INR, and APTT in the GMH-IVH group were significantly higher than those in the non-GMH-IVH group ($P<0.05$), and elevated INR was an important risk factor for GMH-IVH. This may be due to reduced synthesis of coagulation factors in preterm infants, or may be caused by external pathogenic factors that activate the extrinsic coagulation pathway, leading to massive consumption of coagulation factors. Although the role of immature coagulation function in the pathogenesis of GMH-IVH remains controversial, the increased bleeding risk caused by coagulation disorders is undoubtedly a contributing factor to GMH-IVH occurrence [23]. This study further confirmed that there were significant differences in PT, INR, and APTT levels between the poor outcome and good outcome groups of preterm infants ($P<0.05$), among which elevated INR was an independent risk factor for poor GMH-IVH outcomes.

In the early postnatal period, preterm infants are exposed to various hemodynamic influencing factors that can easily lead to abnormal blood pressure changes, placing them at risk for both hyperperfusion and hypoperfusion brain injury, which may be directly related to GMH-IVH occurrence [24-26]. Previous studies have confirmed that increased BPV may be an early marker of CAR dysfunction and can indirectly assess CBF fluctuations [27]. When cerebral perfusion pressure fluctuations exceed the range of CAR, pressure-passive CBF occurs, leading to intracranial hemorrhage [24-25]. This study found a correlation between GMH-IVH occurrence and BPV ($P<0.05$), and elevated DBP SD was an important risk factor for GMH-IVH in preterm infants, indicating that the greater the BPV, the higher the risk of GMH-IVH. However, whether BPV can predict GMH-IVH prognosis has not been reported. This study found that increased BPV was related to short-term outcomes in preterm infants with GMH-IVH, and elevated DBP SD was also an independent risk factor for poor short-term outcomes of GMH-IVH in preterm infants. Therefore, early intensive blood pressure monitoring and management to avoid blood pressure fluctuations are beneficial for reducing GMH-IVH and its adverse outcomes in preterm infants.

Cranial ultrasound is an important method for detecting GMH-IVH, but there is a risk of early missed diagnosis [28]. This study used clinically common, easily accessible, and simple-to-monitor BPV and coagulation indices to predict preterm infants at risk for GMH-IVH. The results showed that combined INR and DBP SD had a certain early warning effect for GMH-IVH occurrence in preterm infants, with sensitivity of 82.4% and specificity of 79.7%. Therefore, preterm infants with coagulation abnormalities and blood pressure fluctuations require enhanced monitoring and comprehensive management measures to reduce blood pressure fluctuations and improve coagulation function, thereby reducing the risk of GMH-IVH.

GMH-IVH in preterm infants is often asymptomatic or has only non-specific symptoms, making it highly susceptible to clinical missed diagnosis, and there is currently no effective treatment, which increases the risk of poor GMH-IVH prognosis. Severe GMH-IVH is highly associated with poor neurodevelopmental outcomes in preterm infants [29], while the impact of mild GMH-IVH on intellectual and motor development remains controversial [30]. Studies have confirmed that children with grade I-II GMH-IVH have deficits in social behavioral function and learning difficulties [31]. Therefore, it is necessary to emphasize early risk prediction for neurodevelopmental outcomes in preterm infants with GMH-IVH. This study found that elevated INR and DBP SD were important factors affecting short-term outcomes of GMH-IVH, and the combination of both had the largest AUC for predicting poor outcomes of GMH-IVH in preterm infants, at 0.864, with sensitivity of 76.2% and specificity of 90.0%. Therefore, preterm infants with GMH-IVH who have abnormal BPV and INR but no clinical symptoms should also undergo early cranial MRI examination, and timely neurological intervention should be provided for those with increased risk of poor prognosis, with focused follow-up.

The occurrence and development of GMH-IVH is a complex evolutionary process, and intracranial hemorrhage may also affect coagulation status. Coagulation function at birth cannot reflect the trend of coagulation function changes in preterm infants, and dynamic monitoring of coagulation indices is still needed to further demonstrate its impact on GMH-IVH.

In summary, elevated INR and DBP SD are independent risk factors for the occurrence of GMH-IVH and its poor outcomes in preterm infants. Combined detection of INR and DBP SD has certain reference value for early identification and prognosis evaluation of GMH-IVH. Early reduction of blood pressure fluctuations and correction of coagulation function abnormalities after birth may help prevent GMH-IVH and improve prognosis in preterm infants.

Author Contributions: JIANG Lijun and YU Qian were responsible for study design and implementation and manuscript writing; YU Qian was responsible for statistical analysis; YU Qian and WANG Fudong were responsible for data collation; GUO Wei was responsible for study design guidance and manuscript

revision.

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Figure 1 [**Figure 1: see original paper**]: ROC curve of INR, DBP SD, and their combination for predicting GMH-IVH in preterm infants

Figure 2 [**Figure 2: see original paper**]: ROC curve of INR, DBP SD, and their combination for predicting poor outcomes of GMH-IVH in preterm infants

Note: Figure translations are in progress. See original paper for figures.